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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
NGUYEN, QUANG	
ART UNIT	PAPER NUMBER
1636	19

DATE MAILED: 11/06/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/632,149	CUTHBERTSON, R. ANDREW	
	Examiner	Art Unit	
	Quang Nguyen, Ph.D.	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *13-24* is/are pending in the application.

4a) Of the above claim(s) *13-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Claims 13-24 are pending in the present application.

Applicant's election with traverse the invention of Group III (claims 23 and 24) in Paper No. 18 is acknowledged.

Applicant argues basically that the restriction set forth in the Office Action dated 3/11/02 is improper because there is no serious burden on the Examiner to examine claims 13-24 as a whole, particularly all the inventions belong to a single and identical class 514, subclass 44. Applicant's argument is respectfully found unpersuasive because to establish burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature searches using databases such as Pubmed, Biosis, Embases should also be taken into evaluating burden of search. The searches for Groups I-III are not co-extensive because each group requires different starting materials (e.g., a patient with a genetic ocular disease such as retinitis pigmentosa, butterfly-shaped pigment dystrophy of the fovea, or adult vitelliform macular dystrophy of Group I, a patient with ocular lysosomal storage disease of Group II, and a patient with ocular wounds of Group III; as well as different exogenous nucleic acids used to treat the aforementioned patients) and different desired therapeutic endpoints. Different text searches for the aforementioned different groups of patients are required here. Clearly different searches and different issues are involved in the examination of each group. Furthermore, a single distinct patentable invention is examined for a single patent application. Therefore, this is made FINAL.

Accordingly, claims 13-22 are withdrawn from further consideration because they are drawn to non-elected inventions.

Claims 23-24 are examined on the merits herein.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

The claims are drawn to a method of treating an ocular wound or an ocular wound after surgery, said method comprising directly contacting an exogenous nucleic acid and an ocular cell *in situ* under conditions permissive for the direct uptake of said

exogenous nucleic acid by said ocular cell, whereby said exogenous nucleic acid is expressed in said ocular cell.

The specification teaches by exemplification showing that upon superficial epithelial debridement (surgical removal of superficial epithelial cells) and topical application of a recombinant replication-defective adenoviral virus expressing β-galactosidase on the treated corneal surface for 30 minutes, extensive β-galactosidase expression was noted in the corneal epithelial cells of treated rats. Similarly, the specification teaches that upon injecting a recombinant replication-deficient adenovirus expressing β-galactosidase into the anterior chamber of the eye, positive staining for the majority of cells lining the posterior surface of the cornea or the corneal endothelial cells was observed for treated rats. Upon injection of the same recombinant adenovirus into the vitreous humor of the eye of treated rats, positive staining for some of the cells of the choroid (a vascular coat surrounding the posterior part of the eye) was detected, indicating β-galactosidase expression in those cells.

The above evidence has been noted and considered. However, the evidence is not reasonably extrapolated to the instant claimed invention that is drawn to methods of treating an ocular wound simply by directly contacting an exogenous nucleic acid and an ocular cell *in situ* under suitable conditions so that the exogenous nucleic acid is expressed in the contacted ocular cell, for the following reasons.

The nature of the instant claimed invention falls within the realm of gene therapy. The specification is not enabled for the instant invention because at the effective filing date of the present application (October 31, 1994), gene therapy was an immature and

highly unpredictable art. This is supported by the report of Orkin et al. (Report and recommendations of the panel to assess the NIH investment in Research on gene therapy, pages 1-40, 1995) to the Director of NIH on the status of gene therapy. The report states "While the expectations and the promise of gene therapy are great, clinical efficacy has not been definitely demonstrated at this time in any gene therapy protocol, despite anecdotal claims of successful therapy and the initiation of more than 100 Recombinant DNA advisory Committee (RAC)-approved protocols", and "Significant problems remain in all basic aspects of gene therapy. Major difficulties at the basic level include shortcomings in all current gene transfer vectors and an inadequate understanding of the biological interaction of these vectors with the host", and "Interpretation of the results of many gene therapy protocols has been hindered by a very low frequency of gene transfer, reliance on qualitative rather than quantitative assessments of gene transfer and expression, lack of suitable controls, and lack of rigorously defined biochemical or disease endpoints" (See pages 1-2 of the report). Even many years after the effective filing date of the present application, Dang et al. (Clin. Cancer Res. 5:471-474, 1999) still state "This workshop reviewed some recent advances in gene delivery, gene expression, immune manipulation, and the development of molecular targets and stressed that all of these fields will need further advancement to make gene therapy a reality" (page 471, col. 1, last sentence of first paragraph). It has been noted that there are several factors limiting an effective gene therapy, and these include suboptimal vectors, a lack of a stable *in vivo* transgene expression, and an efficient gene delivery to target tissues or cells. This indicates that

obtaining therapeutic effects (for this instance wound healing effects) through a gene therapy approach was unpredictable even in 1999, let alone in 1994.

The claims encompass treating an ocular wound (including an ocular wound after surgery or as a result of any ocular disease or any ocular infection) anywhere in the eye and that a broad scope of treating includes the reversion of an injured ocular cell or tissue to its original state by simply directly contacting any exogenous nucleic acid and any ocular cell (e.g., cells of the lens, the cornea, the iris, the retina, choroids, sclera, ciliary body, ocular muscle cells, optic nerve, ocular sensory, motor and autonomic nerves) under suitable conditions so that the ocular cell expresses the exogenous nucleic acid and whereby the ocular wound is treated. The instant specification is not enabled for such a claimed invention. Apart from the exemplification showing the expression of β-galactosidase in corneal epithelial cells, corneal endothelial cells and some of the cells of the choroids, the present disclosure fails to provide any evidence indicating that any therapeutic effects could be achieved for healing any ocular wound, particularly in light of the unpredictable attainment of any therapeutic effects via gene therapy at the effective filing date of the present application as discussed above. The specification fails to provide any specific guidance and any relevant *in vivo* example (part of guidance) demonstrating that any beneficial wound healing effect (e.g., accelerating the ocular wound healing process or alleviating symptoms associated with an ocular wound) has been attained anywhere in the eye. In addition to the unpredictability of the gene therapy art, modulating the wound healing process to attain beneficial therapeutic effect is not routine because the wound healing process involves

many complex molecular and cellular events, such as the inflammatory, proliferative and the remodeling phases requiring different cell types (neutrophils, monocytes, macrophages, fibroblasts as well as endothelial cells) in a spatial and temporal manner (Cordeiro et al., Br. J. Ophthalmol. 83:1219-1224, 1999). On the basis of the instant disclosure, apart from a cursory teaching of using transforming growth factor β (TGF-β) in corneal epithelial wounds (see specification on page 15, lines 14-15), it is unclear what other proteins would be useful in the treatment of ocular wounds, and to which ocular cell populations should an exogenous nucleic acid encoding TGF-β should be contacted in order to attain the desired therapeutic effects for treating an ocular wound anywhere in the eye given a diversity of tissues and cell types in the eye. There is also no evidence in the present application or in the prior art at the effective filing date of the present application, indicating or suggesting that TGF-β could be a "master therapeutic protein" for treating any ocular wound anywhere in the eye simply by expressing its expression in any ocular cell population. Additionally, it is uncertain whether an effective expression level of TGF-β could be attained in the desired ocular cell population, and whether TGF-β expression could be restricted only to the desired ocular cell population. As discussed previously, a low frequency of gene transfer and expression as well as the lack of *in vivo* vector targeting are some of the factors contributing to the unpredictability in attaining therapeutic effects via gene therapy. Moreover, even in the case of TGF-β expression in ocular cells, the instant specification offers no guidance on how to control such expression, such that an inappropriate expression of TGF-β would not occur and results in the scarring and degeneration of

ocular tissues which would defeat the therapeutic effects contemplated by Applicant. With the lack of sufficient guidance provided by the present disclosure for a skilled artisan on the numerous issues discussed immediately above, the simple qualitative β-galactosidase expression detected in various ocular cell populations is not reasonably correlated to the therapeutic effects contemplated by Applicant for treating any ocular wound, and therefore it would have required undue experimentation for a skilled artisan to make and use the instantly claimed invention.

Moreover, the physiological art is also recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Accordingly, due to the lack of guidance and examples provided by the instant specification regarding to the issues set forth above, the unpredictable nature of the gene therapy art as well as complexity of the wound-healing process, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the claimed invention at the effective filing date of the present application.

Examiner would like to note that previous Applicant's arguments are not related to the present claims that are drawn to methods of treating an ocular wound by directly contacting an exogenous nucleic acid with an ocular cell *in situ*.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (703) 308-8339.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, Dave Nguyen, may be reached at (703) 305-2024, or SPE, Irem Yucel, Ph.D., at (703) 305-1998.

Any inquiry of a general nature or relating to the status of this application should be directed to Patent Analyst, Tracey Johnson, whose telephone number is (703) 305-2982.

Quang Nguyen, Ph.D.

DAVE T. NGUYEN
PRIMARY EXAMINER